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DOCUMENT-IDENTIFIER: US 6463438 B1
TITLE: Neural network for cell image analysis for identification of abnormal cells

Abstract Text (1):
A neural network is used in a system to detect abnormalities in cells, including cancer in bladder tissue cells. The system has an image analysis system for generating data representative of imaging variables from an image of stained cells. The set of data is provided to a neural network which has been trained to detect abnormalities from known tissue cells with respect to the data from the same set of imaging variables. A conventional sigmoid-activated neural network, or alternatively, a hybrid neural network having a combination of sigmoid, gaussian and sinusoidal activation functions may be utilized. The trained neural network applies a set of weight factors obtained during training to the data to classify the unknown tissue cell as normal or abnormal.

Brief Summary Text (2):
The present invention relates, in general, to automated image recognition, and more particularly, to a neural network-based image recognition system for cancerous tissue cell detection.

Brief Summary Text (6):
Significant progress in the detection and isolation of bladder tumor specific antigens has linked bladder cancer with an elevation of normal protein components in the plasma or urine of cancer patients. Thus, bladder cancer may be detected by identifying the abnormal presence of materials in the bladder cells. Since these tests are non-invasive, they could be routinely utilized to test those in high risk groups for early symptoms of bladder cancer. However, an approach using serum and plasma related components in urine appears to have limited usefulness in the early detection of bladder cancer as many of these identical components are also present in increased concentrations in urine from patients with non-neoplastic disease.

Brief Summary Text (8):
Due to the vast amount of data to be processed, automation of the bladder cancer cell detection process is quite desirable. Various techniques have been proposed for the automated detection of cancer. Predominately, these prior attempts have relied on techniques such as feature extraction, template matching and other statistical or algorithmic methods. For instance, Melder and Koss described a decision tree representing the hierarchical classification scheme to classify extracted features from the triage of objects encountered in the urinary sediment. Karl K. Melder & Leopold G. Koss, "Automated Image Analysis in the Diagnosis of Bladder Cancer," 26 Applied Optics 16, 3367 (1987). Melder and Koss discussed the use of step-wise linear discriminant analysis in which features were automatically selected for the discriminant functions based on the pooled covariance matrix of more than sixty (60) cell features. Christen, et al., discussed the application of a linear discriminant model from the SPSS/PC+ statistical package to the classification of cancerous cells. Christen, et al., "Chromatin Texture Features in Hematoxylin and Eosin-Stained Prostate Tissue," 16 Analytical and Quantitative Cytology and Histology, 16, 383 (1993).

Brief Summary Text (9):
Recently, artificial neural networks have been applied to the cancer detection process. This step is a logical extension of the pattern recognition capability of

artificial neural networks. Kunihiko Fukushima, "Neural Network Model for Selective Attention in Visual Pattern Recognition and Associative Recall," 26 Applied Optics 23, 4985 (1987); Dwight D. Egbert, et al., "Preprocessing of Biomedical Images for Neurocomputer Analysis," IEEE Int'l Conference on Neural Networks I-561 (Jul. 24-27, 1988).

Brief Summary Text (13):
Traditional back-propagation neural networks have been applied to bladder cells in Ciamac Moallemi, "Classifying Cells for Cancer Diagnosis Using Neural Network," 6 IEEE Expert 6, 8 (1991). Moallemi describes the application of a conventional neural network in the classification of noisy particles versus cell images, including cancerous and non-cancerous bladder cells. However, Moallemi does not teach the detection of malignant cells using a neural network.

Brief Summary Text (14):
The application of neural networks to the classification of cytological specimens is discussed in U.S. Pat. No. 4,965,725 to Rutenberg. Rutenberg describes the use of a two-staged classifier system. The first classifier is a statistical classifier which identifies cell nuclei of interest by measurement of their integrated optical density, or nuclear stain density, defined as the sum of the pixel gray values for the object. Rutenberg discloses that, compared to normal cells, malignant cells tend to possess a larger, more densely staining nucleus. Based on the data provided by the primary classifier, Rutenberg further employs a neural network as a secondary classifier for evaluating the nucleus and its surrounding cytoplasm based on the observation that the ratio between the nucleus and the cytoplasm is an important indicator for malignant cell classification. However, Rutenberg does not utilize other predictive information such as the pgDNA value of a cell.

Brief Summary Text (22):
In accordance with yet another aspect of the invention, a neural network is provided which detects cancerous cells by analyzing raw images of the cell and providing the imaging information derived from the pixels of the images to a neural network.

Brief Summary Text (23):
In accordance with yet another aspect of the invention, a neural network is provided which performs recognition of cancerous cells using information derived from an image of the cells, among others, the area, the average intensity, the shape, the texture, and the DNA content (pgDNA) of the cells.

Brief Summary Text (24):
In accordance with yet another aspect of the invention, a neural network is provided which performs such recognition of cancerous cells using textural information derived from an image of the cells, among them angular second moment, contrast, coefficient of correlation, sum of squares, difference moment, inverse difference moment, sum average, sum variance, sum entropy, entry, difference variance, difference entropy, information measures, maximal correlation coefficient, coefficient of variation, peak transition probability, diagonal variance, diagonal moment, second diagonal moment, product moment, triangular symmetry 11 and blobness.

Detailed Description Text (2):
FIG. 1 illustrates the image analysis 10 of the present invention. Initially, extracted unknown tissue cells are obtained from patients either from urine or a bladder wash. The urine or bladder wash at station 12 is poured through a urine/bladder wash filter 14 and cells are collected on the filter. The cells from wash filter 14 are placed on a slide 17 treated with poly-L-lysine and pressed gently to transfer cells to the slide as an imprint. The cells may also be placed on slides by means of a cytocentrifuge to ensure a reasonably flat distribution of cells with relatively few overlaps.

Detailed Description Text (23):
After the cells have been chemically prepared, the first stage in the analysis of tissue cells for signs of cancer is the cell image acquisition in which the image of the sample tissue cell is digitized and separated from its background. The operation of the image analysis system 10 is described in more detail below.

Detailed Description Text (24):
After the cells have been chemically prepared, an image of the region of interest 16 of the slide 17 containing the sample cells is captured and converted into data files using image acquisition system 18. Essentially, the slide 17 containing the sample cells is illuminated and a video camera in image acquisition 18 is focused on the chosen area in such a way that the frame occupies a maximal area of the screen of a monitor connected to the camera output. The output of the video camera is connected to a video digitizer 20, which converts the video encoding of an image into a raster (bit-mapped) format that can be processed by a computer.

Detailed Description Text (25):
In one preferred embodiment, the CAS-200 RTM image analysis hardware and software (available from Cell Image Systems, Elmhurst, Ill.) provides intensity information (at 8 bits per pixel) and a 256.times.256 pixel image, with a resolution of approximately 0.3 micron to 0.5 micron per pixel and a 229 gray scale resolution. In another preferred embodiment, the Zeiss-IBAS RTM rapid scanning image analysis system (available from Roche Image Analysis Systems) provides a 1280.times.1024 image, with a 255 gray scale capability.

Detailed Description Text (26):
Because the conversion equipment alters the horizontal scale factor, in order to restore the aspect ratio distortion to 1:1, the original images are expanded horizontally by a factor of 1.78. After the aspect image ratio distortion correction, the cell images are tailored into an array of pixel images. The cell images are centrally aligned in this area. In the case of a large image, the image is clipped to fit into the given cell size within the boundary.

Detailed Description Text (27):
In this manner, three sets of bladder cell images were obtained for classification by the neural network. Two sets of images were fluorescent-labeled with the M-344 monoclonal antibody directed against a p300 bladder tumor associated antigen demonstrated to have clinical utility in identifying low grade bladder cancer cells in cytology specimens. One set of sixty (60) M-344 cell images were obtained at 32.times. in a 60.times.60 pixel array and included positive and false-positive images. The second set of eight hundred (800) M-344 cell images were collected at 12.5.times.magnification. Both sets of M-344 images were collected using an automated Zeiss-IBAS rapid scanning image analysis system. The third set of images covered the absorbance set of 467 cell images taken at 40.times.magnifications of Feulgen stained cells. Images of the third set were captured using the CAS-200 image analysis system.

Detailed Description Text (28):
In pattern recognition, only discriminate information contributes to correct classification, while information unrelated to the identification process does not and may even degrade performance. To reduce the input data and to focus the neural network on relevant variables, a pre-processing step is applied to extract cellular features from the raw image. Feature generation processing is used to extract information on the area, average intensity, shape (roundness), texture and pgDNA values. In the preferred embodiment, an image analysis system 10 is used to extract the list of imaging variables from the digitized images. These imaging variables are stored in an input vector consisting of the following:

Detailed Description Text (37):
Texture describes the interdependent characteristics of pixels within a neighboring area. Regular texture has more or less periodical patterns, while random texture is best described by its "coarseness." In the preferred embodiment, texture is measured by a convolution using a 3.times.3 mask for extracting high frequency information (high pass filtering) from an image. The mask resembles a Laplacian kernel, commonly used for edge sharpening. Preferably, the filter G has a convolution mask of:
##EQU4##

Detailed Description Text (38):
This convolution mask is applied across every pixel in the interior area of a cell image, not including background. The texture for a particular cell can be obtained

as follows: ##EQU5## where O(i,j) is the convolution output at location (i,j) on a cell image. G(i,j) corresponds to the intensity value at the location (i,j). .pi. represents the 8 neighboring locations of (i,j).

Detailed Description Text (41):
In one embodiment, twenty-one nuclear descriptions based upon the gray-level transition probabilities of Feulgen stained nuclei are provided by the CAS System. The CAS constructs a "Markovian" matrix from a normalized cell nucleus image using an operator selected step size ranging from 1 pixel to 254 pixels. The step size defines the size of the "grain" (in number of pixels) which is to be compared to the neighboring "grains". The default step size in the CAS System is 1 pixel, which was the step size used (i.e. every grain is equal to 1 pixel). In addition, each cell nucleus image is normalized by partitioning the image into eight equally frequent gray-levels, each level consisting of an equal number of pixels. This normalization process is done by first plotting the optical densities (gray-levels) above the operator set threshold against the number of pixels. This plot is divided into eight gray-level ranges (optical density ranges) which contain an equal number of pixels. This results in a normalized cell nucleus image consisting of gray-level values from 0-7.

Detailed Description Text (42):
An 8.times.8 gray-level transition matrix is constructed from the normalized cell nucleus image by comparing the gray-levels of neighboring "grains" (i.e. if a given "grain" has a normalized value of 4, and its neighboring "grain" has a normalized value of 3, an entry in the matrix is made at location Row-r and Column-3). This matrix is then transformed into an 8.times.8 conditioned gray-level transition probability matrix by dividing every matrix entry by the total number of pixels in the cell nucleus image. This "Markovian" probability matrix is then used to compute the plurality of Markovian texture features.

Detailed Description Text (46):
The pixel measurements within the cell object, if properly calibrated to represent optical density, relate the resulting values to such cell constituents such as the total amount of DNA in nucleated cells, the amount of monoclonal antibody attached to nuclear or cytoplasmic receptor cites, etc. In the instant invention, the measurements are calibrated to reflect the mass in picograms of these cell constituents. The DNA measurements are carried out on Feulgen stained preparations using optical density at a wavelength of 620 nm and with 256 gray scale levels.

Detailed Description Text (47):
Each digitized image field may be described as a function n(x,y), where each value is a measured point of absorbance obeying the Beer-Lambert absorption law: ##EQU8##

Detailed Description Text (48):
where I.sub.o is the incident light, I.sub.t is the transmitted light, .epsilon. is the specific extinction coefficient of the absorbing substance (.mu.m.sup.2 /pg) at a chosen wavelength (.lambda.) and with a specific bandpass (b), m is the mass of the absorbing substance in picograms (pg) for each x,y image field measurement point inside the object or cell, and a is the measurement spot size in (.mu.m.sup.2). Assuming the boundary points have been properly determined for a single cell in the field of view, where the summation occurs only over the cell or cell part of interest, ##EQU9##

Detailed Description Text (50):
Converting from transmitted light to optical density is necessary because the thickness of the object cells, or cell parts, can vary. This causes the light transmitted through any individual pixel to fall off exponentially as a function of the object thickness. The logarithm of the transmitted light converts this exponential function to a linear function and properly allows the summation of the pixels, whether they result from a part of the cell that is thinly spread or thickly condensed.

Detailed Description Text (51):
After the features have been extracted from images cell by cell, computer 22 creates a feature vector data list. Items on the feature list are then normalized by their

corresponding standard deviations to prevent certain features that have substantially larger numerical values than others from dominating the training process. Even after normalization, certain cells still have feature values out of the transition region, beyond which is a saturated region of activation function. To keep the feature value within the transition region, a scaling factor is used in the activation function of neurons on the texture processing.

Detailed Description Text (52):
Once the feature vector is derived from the image acquisition system, the data is then processed by a neural network 30. A Sun,Sparcstation IPC workstation is used to train and test the neural network. The neural network 30 selected for the preferred embodiment of the present invention is a hybrid multilayer feed forward perceptron with error back-propagation training algorithm. The neural network 30 differs from conventional neural networks in that its architectural makeup consists of neuron elements with differing activation functions.

Detailed Description Text (57):
The input layer 40 of the present invention comprises a plurality of nodes 42, 44, 46 and 48, which are configured to receive input information from a computer 22 outside of the neural network 30. The nodes of the input layer store data to be forward propagated to the neurons of the hidden layer 50. A hidden layer 50 comprising a plurality of neurons 52, 62 and 72, accepts as input the output of the plurality of neurons 42, 44, 46 and 48 from the input layer 40. The neurons of the hidden layer 50 transmit its outputs to a plurality of neurons 92 and 100 in the output layer 90. The output layer 90 comprises a plurality of neurons 92 and 100 that are configured to transmit an output pattern to an output source outside of the artificial neural network 30. One preferred embodiment employs 3,600 neurons in the input layer plus one neuron which holds a bias value to analyze the pixel information from the raw image of the cell. A second preferred embodiment employs five neurons in the input layer plus one bias neuron for analyzing an array of composite imaging variables of each cell. The second approach reduces the amount of information that must be processed by the neural network and thus improves the throughput of the neural network although at the expense of pre-processing computations. The neuron supplying the bias value is set to a constant value, such as one (1).

Detailed Description Text (60):
Referring now to FIG. 4, neuron 52 receives inputs from a plurality of nodes 42, 44, 46 and 48. The interconnection between nodes 42, 44, 46 and 48 and neuron 52 have a plurality of weight factors 114, 116, 118 and 120 which adjust the value of the data coming from nodes 42, 44, 46 and 48. Weight factors 114, 116, 118 and 120 may be built from variables which can attenuate the incoming information appropriately. The inputs and the bias are supplied to multipliers which accept another input from a weight factor vector. Outputs from the multipliers are supplied to an adder unit for computing the weighted sum of the input values. In essence, the neurons perform a dot product of a vector of the weighted input values, including a bias value, with a vector representing the weights. The output value from the adder is passed through a non-linear function (sinusoid, sigmoid or gaussian) to generate a single neuron output value. The output of each neuron 52 in the input layer is propagated forward to each input of each neuron in the next layer, the hidden layer. In the case where the raw image data is fed directly to the neural network, the neurons of the input layer 40 scans 3,600 inputs which are neighboring input pixels, or gray values from an image. When the imaging variables are used, neurons of the input layer 40 scans its five input nodes. The feature inputs can be presented in any order. However, the order of presentation must match the order used for training. In using raw image data, the 3,600 gray scale levels are presented starting from upper left corner scanning to the right lower corner of the image. Using composite imaging data, the order of training data presentation must match the order used during the unknown sample data presentation.

Detailed Description Text (85):
The network was first trained using data from the CAS-200 image analysis system. Table 1 reports the test results and overall classification rate on a 98 cell set. Values listed in Table 1 for each test run are: (1) the network output value; and (2) the square of the deviation [(error) .sup.2 ] from the desired target output. An

output of indicates abnormality, while "0" indicates normal cell structure.

Detailed Description Text (86):
Table 1 results indicate that the network trained by raw cell images were capable of correctly classifying 72% of the test cells. However, using extracted features such as the features of area, intensity, texture and shape, the network was able to correctly classify 93% of the sample images. These data are most encouraging considering the fact that several low grade bladder carcinoma cells were included in the abnormal cell array. The positive results are most comparable if not better than those obtainable by an expert cytopathologist.

Detailed Description Text (88):
The set of samples of M-344 cells was tested in three different configurations. In the first configuration, fifty percent (50%) of M-344 positive, negative and noise cell data were allocated for training, and the rest of data, including the entire false positive data, were used for testing. The individual classification results and overall rate were analyzed and the misclassified cells were determined. The threshold used for classification is 0.5. It was found that the feature vector trained network results in a higher average (taking all four groups into account) classification rate than the raw image trained one, 75.5% versus 69.8%. The score for false positive data is low, at about 55.7% and 57.6% for feature vector and raw image, respectively. But when calculated only for positive, negative and noise data, the classification rate increases to 88.4% and 77.8%.

Detailed Description Text (90):
Neural networks were also studied in a third configuration when only positive and false-positive M-344 data are presented. Data were allocated evenly between training and testing. Next when only positive and false-positive were calculated, there was an increase in overall classification rate compared with configuration 1 for both feature vector and raw image trained networks. However, as far as the effect of false-positive cell identification participation of training is concerned, the results are consistent with that from configuration 2.

Detailed Description Text (91):
Turning now to a more in-depth discussion of the present invention with specific reference to FIG. 1, the screening device is shown with particular emphasis on the classification elements embodied in the processing system. In the preferred embodiment, the processing system includes an image processor with digitizer and a neural network implemented on a general purpose processor. For improved recognition speed, the neural network can be implemented in hardware.

Detailed Description Text (92):
The general processor is preferably a Sun SPARC IPC workstation although it may be another computer-type device suitable for efficient execution of the functions described herein such as an Intel Pentium or a Motorola PowerPC class computer system. The general processor controls the functioning of and the flow of data between components of the device, may cause execution of additional primary feature extraction algorithms, and handles the storage of image and classification information. The general processor additionally controls peripheral devices such as a printer, a storage device such as an optical or magnetic hard disk, a tape drive, etc., as well as other data collection devices.

Detailed Description Text (94):
It will be appreciated by a person of ordinary skill in the art that, while particular resolutions and image sizes were described above, these particular values are exemplary. It will further be appreciated that different resolutions, image parameters, magnification levels, etc., can be employed to accomplish the same or similar results as the particular embodiment of the invention described above, and that all such differing resolutions, image parameters, imaging variable data items, neuron count, etc. are within the scope of the present invention.

Detailed Description Text (95):
It should be further recognized that, although the preferred embodiment describes a neural network with one hidden layer, a plurality of hidden layers may be used. Also, different number of neurons may be used in input, output or hidden layers. In

addition, it should further be recognized that while the image processor with digitizer and the general processor are described operating in a serial manner, in actual practice as many functions will be performed in parallel as is possible. Hence, the components may process different slide segments or different areas of a segment concurrently, greatly reducing the time required to screen a sample. L/C"v" ##SPC1## ##SPC2## ##SPC3## ##SPC4## ##SPC5## ##SPC6## ##SPC7## ##SPC8## ##SPC9## ##SPC10## ##SPC11## ##SPC12## ##SPC13## ##SPC14## ##SPC15## ##SPC16## ##SPC17## ##SPC18## ##SPC19## ##SPC20## ##SPC21## ##SPC22## ##SPC23## ##SPC24## ##SPC25## ##SPC26## ##SPC27## ##SPC28## ##SPC29## ##SPC30## ##SPC31## ##SPC32## ##SPC33## ##SPC34## ##SPC35##

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